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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,901	ZAGHOUANI, HABIB	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-22,26-59 and 62-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-22, 26-59, and 62-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendment April 11, 2006 are acknowledged.

Claims 1-18, 23-25, 60, 61, and 66-68 have been canceled.

Claims 19, 34, 49, 64, and 65 have been amended.

Claims 19-22, 26-59 and 62-65 are pending and under examination in this office action.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 19-22, 26-59, and 62-65 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 10/277,264 for the reasons of record set forth in the office actions mailed July 23, 2004, June 16, 2005, and January 10, 2006.

Applicant's arguments filed April 11, 2006 have been fully considered but they are not persuasive. Applicant repeats arguments more fully developed in the response

received October 14, 2005, and the examiner's response is as was set forth in the office action mailed January 10, 2006.

Therefore, the rejection has been maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 19-22, 26-59, and 62-65 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 10/847,139 for the reasons of record set forth in the office action mailed January 10, 2006.

Applicant has not responded to this rejection in the arguments received April 11, 2006. The rejection is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 19-22, 26-59, and 62-68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of copending Application No. 10/681,788 for the reasons of record set forth in the office action mailed January 10, 2006.

Applicant has not responded to this rejection in the arguments received April 11, 2006. The rejection is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 19-22, 26-59, and 62-65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 11/290,070 for the reasons of record set forth in the office action mailed January 10, 2006.

Applicant has not responded to this rejection in the arguments received April 11, 2006. The rejection is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 34-39, 41-54, 56-59, and 62-65 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the reasons of record set forth in the office actions mailed July 23, 2004, June 16, 2005, and January 10, 2006.

Applicant's arguments filed April 11, 2006 have been fully considered but they are not persuasive. Applicant argues that the amendment of the claims to recite that the epitopes are specific for autoreactive T cells associated with said autoimmune disease, rather than merely involved in said autoimmune disease, and that the claims are now structurally and functional limited to involve only particular autoimmune diseases necessitates the removal of the rejection of record.

The rejection of record indicated that the claims did not read on particular autoimmune diseases and that there was no written description of all the antigens and epitopes associated with all autoimmune diseases. Applicant's amendments have exacerbated these problems and it is unclear why applicant believes that the rejected claims are only limited to specific autoimmune diseases. First, the specific autoimmune diseases multiple sclerosis, type 1 diabetes mellitus, and rheumatoid arthritis are not limitations of the claims rejected above (although they are limitations of claims 19-22, 26-33, 40, and 55) and as such the claims are not limited to particular autoimmune

diseases. As was discussed in the rejections of record, the application does not provide a written description of all epitopes recognized in all autoimmune diseases, or even a representative number of examples that support the breadth of the term autoimmunity. Second, the preamble to independent claims 34, 49, and 64 recite methods of reducing diseases and does not recite a method of treating autoimmune diseases. The recited T cell epitope is limited to those epitopes specific for autoreactive T cells of an autoimmune disease, but is not recited that the disease of the preamble is an autoimmune disease or that the recited antigen is specific for autoimmune diseases. As such, applicant has claimed a method of treating any disease characterized by the need for an increase in the level of IL-10 or a reduction in the level of IFNγ and has thereby broadened, rather than reduced the scope of the invention for which patent protection is being sought. Applicant is not in possession of the full breadth of methods of administering immunoglobulins comprising epitopes recognized by autoreactive T cells that have been substituted into a CDR of an immunoglobulin for the treatment of all diseases or all autoimmune diseases because the identity of all of the antigens and epitopes recognized by autoreactive T cells are not known and the identity of these unknown antigens and epitopes cannot currently be predicted. As such, the rejection is maintained.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 34-37, 43-52, and 58-65 stand rejected under 35 U.S.C. 102(b) as being anticipated by Zanetti et al. (WO 90/09804A1, of record, see entire document), for the reasons of record.

The office action mailed July 23, 2004, states that:

The '804 patent teaches treating autoimmunity by administering Ig fusion proteins with antigens associated with autoimmunity to induce tolerance, wherein said antigens are placed in the CDR3 region of IgG molecules. It is noted the steps of identifying an individual in need of increased IL-10 or decreased IFN-gamma, have been read to include treating any person with an inflammatory disease since a person with an inflammatory disorder would need an increase in IL-10 a known Th1 inhibitor or a decreased IFN-gamma a known Th1 mediator.

The claimed invention is anticipated by the prior art.

Applicant argues that:

"[T]he Ig fusion construct of the present invention, as currently amended, is a distinct structure to that described in Zanetti, as the Ig protein of the present invention must have the CDR removed and replaced with a T cell epitope specific for autoreactive T cells associated with a particular autoimmune disease. The level of specificity described in the claims now provides the necessary structural limitations which obviate the present invention from that described in the art." (Section 4, page 10 of the 4/11/06 response)

This argument is unpersuasive. As was explained in greater detail in the office action mailed January 10, 2006, Zanetti et al. clearly teach on line 24 of page 22 that the peptide epitope is to be inserted or *substituted* for a CDR sequence. Thus, Zanetti et al. do teach the removal of CDR3 and its replacement with a T cell epitope, and the rejection is maintained.

11. The rejection of claims 19-22, 28, 29, 32-40, 43, 44, 47-55, 58, 59, and 62-65 under 35 U.S.C. 102(b) as being anticipated by De Boer et al. (WO 95/32734A1, see entire document) has been withdrawn in light of applicant's claim amendments received April 11, 2006. Specifically, De Boer do not teach an immunoglobulin that comprises a T cell epitope in the location normally occupied by a complementarily determining region (CDR) in their methods of treating autoimmune disorders. This structural limitation is present in all pending claims and therefore the rejection has been withdrawn.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 19-22, 28-40, 43-55, 58, 59, and 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Boer et al. (WO 95/32734A1, of record, see entire document) in view of Zanetti et al. (WO 90/09804A1, of record, see entire document) for the reasons of record.

The office action mailed January 10, 2006 states that:

De Boer et al. teach compositions and methods for treating autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and type I diabetes mellitus (see entire document, particularly the abstract and lines 14-18 of page 22). The compositions used in these methods of treatment consist of an antigen combined with an agent capable of crosslinking Fc_γ receptor molecules (see particularly lines 6-25 of page 14). Antigens disclosed for use include disease autoantigens (see particularly lines 3-5 of page 15), and the Fc receptor crosslinking agent can be aggregated human IgG, Fc domains of human IgG, bi- or multivalent anti-Fc_γ receptor monoclonal antibodies or active fragments thereof, and recombinant fusion proteins (see particularly the abstract, the paragraph that spans pages 11 and 12, and claims 1-35). The antigen and Fc receptor crosslinker are disclosed as being attached or aggregated by any technique known in the art, such as covalent chemical crosslinking and the generation of recombinant fusion proteins (see particularly lines 10-15 of page 14 and lines 14-16 of page 15). These reagents are also disclosed as being immobilized in a lipid matrix (see particularly lines 23-31 of page 13).

Note that the instant application defines chimeric more broadly than what is customary in the art, such that any fusion protein comprising an Fc domain and a heterologous sequence, such as an antigen, is considered by applicant to be a "chimeric antibody" (see particularly the paragraph that spans pages 38 and 39 of the instant specification). As such, the fusion polypeptides disclosed by De Boer are "chimeric antibodies." It is also noted that some of the instant claims indicate a need to identify individuals in need of increased levels of IL-10 or in need of reduced IFNγ, and that the art of De Boer does not appear to discuss these cytokines. However, the instant specification discloses that IL-10 inhibits the activity of T cells specific for multiple epitopes involved in autoimmune diseases, and as such any person suffering from a Th1 mediated autoimmune disease is in need of increased IL-10 (see particularly the paragraph that spans pages 44 and 45). Further, it is well known in the art that IL-10 is an inhibitor of Th1 cytokines, that IFNγ is a Th1 cytokine, that Th1 cytokines are involved in inflammatory immune responses, and that the destruction of myelin sheaths in MS, synovium erosion in rheumatoid arthritis, and islet cell destruction in type I diabetes mellitus are all inflammatory reactions. As such, a medical diagnosis that a patient has multiple sclerosis, rheumatoid arthritis, or type I diabetes mellitus inherently identifies individuals that need increased IL-10 and decreased IFNγ.

These teachings differ from the instant claimed invention in that while De Boer et al. teach methods of treating autoimmune diseases using conjugates comprising an Fc receptor crosslinker and an autoantigen, they do not indicate that the autoantigen is to be located in the CDR3 loop of an antibody.

Zanetti et al. teach that the introduction of an antigen into the CDR3 loop of an antibody offers the advantage of a construct that maintains immunoglobulin constant domain functionality yet contains novel epitope reactivity with the CDR3 loop being preferred because it is surface exposed and is structurally plastic since it is known to naturally contain sequences of diverse length and amino acid composition (see entire document, particularly the abstract, lines 7-25 of page 5, and the paragraph that spans pages 10 and 11).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to insert autoantigens into the CDR3 lops of the constructs disclosed by De Boer et al. in order to gain the advantages of maintained constant domain effector function, epitope reactivity, structural plasticity and surface exposure of the autoantigen epitope as taught by Zanetti et al.

Applicant argues that the structural limitations present in the claims as amended April 11, 2006 are not taught by either the primary or secondary reference, and therefore the rejection has been obviated. The structural limitations of the immunoglobulins administered as part of the instant methods are taught by Zanetti et al. as has been discussed above and in prior office actions. Applicant has provided no additional arguments as to why these references are improperly combined. Note that claims 20-22, 28, 29, 32-40, 43, 44, 47-55, 58, 59, and 62-65 have been joined to this rejection based upon applicant's amendments which recite additional structural limitations in the independent claims which are not taught by De Boer et al. in isolation but that are rendered obvious in view of Zanetti et al. Claims 19-22, 28, 29, 32-40, 43, 44, 47-55, 58, 59, and 62-65 were previously rejected based upon De Boer alone, and the addition of these claims to the rejection of record is both proper and necessitated by applicant's amendments.

The rejection is maintained.

14. The rejection of claims 19, 26, 27, 34, 41, 42, 56, and 57 under 35 U.S.C. 103(a) as being unpatentable over De Boer et al. (WO 95/32734A1, see entire document) in view of Legge et al. (J. Exp. Med. 1997, 185:1043-1053, see entire document) has been withdrawn in has been withdrawn in light of applicant's claim amendments received April 11, 2006. Specifically, De Boer do not teach an immunoglobulin that comprises a T cell epitope in the location normally occupied by a complementarily determining region (CDR) in their methods of treating autoimmune disorders. This structural limitation is present in all pending claims and therefore the rejection has been withdrawn.

The following are new grounds of rejection necessitated by applicant's amendments to the claims received April 11, 2006.

Claim Rejections - 35 USC § 103

15. Claims 19, 26, 27, 34, 41, 42, 49, 56, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Boer et al. (WO 95/32734A1, of record, see entire document) in view of Zanetti et al. (WO 90/09804A1, of record, see entire document) as applied to claims 19-22, 28-40, 43-55, 58, 59, and 62-65 above, and further in view of Legge et al. (J. Exp. Med. 1997, 185:1043-1053, of record, see entire document).

The teachings of De Boer et al. in view of Zanetti et al. have been discussed above. These teachings differ from the instant claimed invention in that while the combination of references teaches methods of treating the disease multiple sclerosis with genetically engineered immunoglobulins comprising a CDR3 that has been replaced with T a cell epitope of an autoantigen, they do not teach epitopes of the specific multiple sclerosis autoantigens proteolipid protein (PLP) or myelin basic protein (MBP).

Legge et al. teach that PLP and MBP are major autoantigens recognized by autoreactive T cells from patients suffering from multiple sclerosis, and provide T cell epitopes that are recognized by said autoreactive T cells (see entire document, particularly the introduction, most particularly the paragraph spanning pages 1043 and 1044). They also teach that the use of autoantigen epitopes in antibody fusion constructs offer the advantage that these autoantigens are presented to the immune system in a manner that is capable of eliciting an immune response to a self antigen (see particularly the discussion and Figures 1-9).

Therefore, a person of ordinary skill in the art at the time the invention was made would have been motivated to insert epitopes of the specific multiple sclerosis autoantigens PLP and MBP as taught by Legge et al. into genetically engineered immunoglobulins comprising a CDR3 that has been replaced with a T cell epitope of an autoantigen as taught by De Boer et al. and Zanetti et al. to gain the advantage of using epitopes of major multiple sclerosis autoantigens known to be recognized by the immune system when presented in a fusion construct comprising an immunoglobulin and said epitope in methods of treating the autoimmune disease multiple sclerosis.

Claim Rejections - 35 USC § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 19-22, 26-59, and 62-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the claims are indefinite because the identity of the antigen recited as being linked to an immunoglobulin in independent claims 19, 34, 49, 64, and 65 is not clear. Is the antigen the recited T cell epitope specific for autoreactive T cells that is located in a CDR or is the antigen something else since an antigen can comprise more than one epitope? Dependent claim 30 recites that the antigen is positioned in a CDR, but since an immunoglobulin comprises 6 CDRs, the immunoglobulin could comprise both an epitope and an antigen. This ambiguity is not addressed by any pending dependent limitation, and as such all claims are indefinite.

Independent claims 34, 49, and 64 recite "said autoimmune disease" and this term lacks antecedent basis because no autoimmune disease is recited previously in the claim. These claims do recite disease, but given that disease is a broader concept that encompasses autoimmune and other diseases, it is not clear to what the recitation of "said autoimmune disease" refers.

18. Claims 34-59 and 62-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has amended the claims to recite a method of reducing the symptoms of disease in an individual by administering an immunoglobulin molecule that comprises a CDR that has been replaced with a T cell epitope specific for autoreactive T cells

associated with an autoimmune disease. The disease that is being treated is not recited. As such, the claims reasonably read on a method of treating all diseases. The specification does not teach or provide working examples that an immunoglobulin comprising a T cell epitope recognized in a particular autoimmune disease, for example multiple sclerosis, has therapeutic efficacy in the treatment of diseases that are other than the autoimmune disease for which the epitope is specific, in this example multiple sclerosis. It is not reasonable that administering a reagent that reduces the immune response present in a patient suffering from multiple sclerosis can be used to treat vastly different diseases such as bacterial or viral infections, with infections and other diseases being encompassed by the breadth of applicant's claims as amended. Given that immune system responses are specific for defined epitopes of antigens, it would require an undue amount of research for a skilled artisan to perform the full scope of applicant's claimed method which reads on administering a single composition to treat all diseases.

19. No claims are allowable.

20. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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June 19, 2006

6/23/06
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